REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The 35 U.S.C. §112 Rejection

Claims 1-4, 6-7, 16, 18-20 and 22 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 1 has been amended to recite an adenovirus that mediates enhanced gene transfer to primary tumor cells, wherein the fiber gene of said adenovirus is modified by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. Enhanced gene transfer to primary tumor cells was demonstrated with ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human

SCCHN cells (Example 33, Figure 25). These data indicate the modified adenovirus can mediate significant enhancement of gene transfer to primary tumor cells through a coxsackievirus and adenovirus receptor-independent pathway. Hence, Applicants respectfully submit that the scope of the claims 1-4 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 1-4 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 16 has been amended to recite a method of increasing the ability of an adenovirus to transduce primary tumor cells by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob of said adenovirus. As discussed above, the specification has demonstrated enhanced gene transfer to primary tumor cells such as ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25) by adenovirus modified with a ligand inserted into the H1 loop. Hence, Applicants respectfully submit that the scope of the claims 16 and 22 in the

instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 16 and 22 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 9, 11-12 and 23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 9 is drawn to an adenovirus modified by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. The claimed modified adenovirus further comprises a herpes simplex virus-thymidine kinase gene. Claim 11 is drawn to a method of using the virus of claim 9 and ganciclovir to kill tumor cells in an individual. Applicants submit that the method of administering adenovirus that carries herpes simplex virus-thymidine kinase gene to an individual followed by ganciclovir treatment is a standard treatment procedure that is currently used in a number of gene therapy trials. Hence, it does not require undue experimentation for one of ordinary skill in the art to practice this method of killing tumor cells. Accordingly, Applicants respectfully request that the

rejections of claims 9, 11-12 and 23 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-4, 6-9, 16, 18-20 and 23 were rejected under 35 U.S.C. §102(e) as being anticipated by **Wickham** et al. The rejection is respectfully traversed.

The present invention is drawn to a modified adenovirus that mediates enhanced gene transfer to primary tumor cells and method of using such modified adenovirus to transduce primary tumor cells. The claimed adenovirus is modified by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. As discussed above, the present invention provides data that show the claimed adenovirus mediates enhanced gene transfer to primary tumor cells (Figures 17, 19, 20, 25). Applicants submit that generation of the claimed adenovirus that mediates enhanced gene transfer to primary tumor cells and the method of using such modified adenovirus to enhance gene transfer to primary tumor cells were not taught or suggested in **Wickham** et al.

The Examiner argued that **Wickham** et al. anticipates the instant claims because **Wickham** et al. taught modification in the HI loop and insertion of nucleic acid sequences encoding RGD peptide and HSV-TK. Applicants respectfully disagree. Applicants submit that **Wickham** et al. only disclosed functional data for adenovirus with RGD inserted at the C-terminus, not the HI loop, of the fiber protein (see Examples 9 and 10). **Wickham** et al. concluded that "these results thus confirm that the RGD peptide motif (i.e. present as a loop at the C-terminus of the fiber protein) ...to target the adenovirus to a new receptor" (column 37, line 26 to column 38, line 7).

Moreover, **Wickham** et al. only disclosed various vectors purported to be useful in generating modified adenovirus, but **Wickham** et al. did not report any functional data that showed a modified fiber protein with RGD inserted into the HI loop could be incorporated in an adenovirus. As the Examiner has pointed out in the instant Office Action, "determination of the effects of particular modifications are not predictable until they are actually made and used; the introduction of ... ligand into the HI loop of the fiber protein is nothing more than a trial and error situation" (instant Office Action, page 4, lines 20-22). Therefore, in view of the lack of data

that indicated an adenovirus with a RGD peptide inserted into the HI loop of the fiber protein was actually made and used in **Wickham** et al., **Wickham** et al. did not provide an enabling disclosure and did not anticipate the present invention.

The Examiner also argued that **Wickham** et al. taught gene transfer into tumor cells. Applicants respectfully disagree. Applicants submit that **Wickham** et al. did not teach or suggest an adenovirus with a RGD peptide inserted into the HI loop of the fiber protein would mediates enhanced gene transfer to primary tumor cells as claimed herein. **Wickham** et al. only disclosed an adenovirus modified by insertion of RGD into the C-terminal of the fiber knob (Example 10). Moreover, **Wickham** et al. only showed gene transfer data in kidney cells, smooth muscle cells and endothelial cells, not tumor cells, by adenoviruses that have RGD inserted into the C-terminal of the fiber knob (Table 3). In contrast, the instant invention presents data and claims a method of using modified adenoviruses that have RGD inserted into the HI loop of the fiber knob to enhance gene transfer to primary tumor cells (Figures 17, 19, 20, 25).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently

described, in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. Since **Wickham** et al. did not teach or suggest each and every aspect of the instant invention, **Wickham** et al. did not anticipate claims 1 and 16 of the present invention. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 6-9, 16, 18-20 and 23 under 35 U.S.C. §102(e) be withdrawn.

This is intended to be a complete response to the Office Action mailed November 23, 2001. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (amended) A recombinant adenovirus that mediates enhanced gene transfer to primary tumor cells, wherein said adenovirus comprises a fiber gene modified by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob.

Claim 16 has been amended as follows:

16. (amended) A method of increasing the ability of an adenovirus to transduce primary tumor cells, comprising the steps of:

modifying the fiber gene of said adenovirus by introducing a ligand comprising a tripeptide having the sequence Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob; and

transducing said primary tumor cells with said adenovirus, wherein said transduction results in enhanced gene transfer to said tumor cells.